REMARKS

Reconsideration of the rejection of the subject applicantion is respectfully requested in view of the above amendments and the following remarks.

Claims 1, 2 and 4 to 10 are present

Claim 1 has been amended to define

X is F, Cl, Br, I or R^1. Basis for this amendment is found in amended Claims 1 and 2, and in the Specification in Example 1 at page 12, Example 3 at page 16, Example 4 at pages 17 and 18, and Example 5 at pages 19 and 20.

It is also to be noted that Claims 1 and 2 have been amended so that X and Y no longer include H.

Claims 1 has been amended to include the oxidoreductase enzyme as defined in original Claim 3.

Claim 2 has been amended to include the microorganism set out in Example 1 at page 14 of the Specification.

New Claim 5 depends from Claim 2 and defines the microorganism as Saccharomyces cerevisiae, which is baker's yeast as disclosed in Table 1 and Example 2 at page 14.

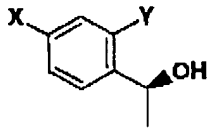
New Claim 6 depends from Claim 2 and defines X as F and Y as Br or R^1. Basis is found in Examples 1 to 5 and in original Claims 1 and 2.

New Claim 7 depends from Claim 6 and defines X as F and R^1 as $(CH_2)_nCOOR^3$ where R^3 is alkyl. Basis is found in original Claims 1 and 2 and in Examples 3 to 5.

New Claims 8 and 10 depend from Claim 1 and define X as F, and Y as Br or R^1 which is $(CH_2)_nCOOR^3$. Bases is found in Example 1 and at page 5, lines 5 and 6 of the Specification.

New Claim 9 depends from Claim 2 and defines X as F and Y as Br. Basis is found in original Claims 1 and 2 and Example 1.

Applicants invention as now claimed in Claims 1 and 2 is defined as a process for the preparation of a compound of Formula (I)



(I)

wherein X is F, Cl, Br, I or R^1; and Y is Cl, Br, I or R^1;

R^1 is substituted or unsubstituted alkyl, alkenyl or $(CH_2)_nCOR^2$;

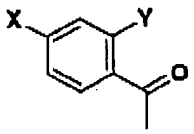
n is an integer from 1 to 10;

R^2 is OH, OR^3 or NH_2; and

R^3 is substituted or unsubstituted alkyl, alkenyl,

C_{3-7} cycloalkyl or substituted or unsubstituted aryl;

by stereoselective reduction of a compound of Formula (II)



(II)

wherein

X is F, Cl, Br, I or R^1; Y is Cl, Br, I or R^1;

R^1 is substituted or unsubstituted alkyl, alkenyl, or $(CH_2)_nCOR^2$;

n is an integer from 1 to 10;

R^2 is OH, OR^3 or NH_2; and

R^3 is substituted or unsubstituted alkyl, alkenyl,

C_{3-7} cycloalkyl or substituted or unsubstituted aryl.

In Claim 1 the reaction of the ketone of Formula (II) is carried out with an oxidoreductase enzyme capable of catalyzing the enzymatic reduction of ketones represented by Formula (II), which enzyme is the *Pichia methanolica* ketoreductase of Figure 1 as expressed in Escherichia coli.

In Claim 2, the ketone II is reacted with a microorganism that supplies an oxidoreductase enzyme capable of catalyzing the enzymatic reduction of ketones represented by Formula (II), which microorganism is set out in Claim 2.

Preferred microorganisms as defined is Claim 4 are selected from the group consisting of *Pichia methanolica* ATCC 56510, *Pichia methanolica* ATCC 56508 and *Pichia methanolica* ATCC 58403, wherein said oxidoreductase is a ketoreductase.

It is submitted that Applicants' process as defined in Claim 1,2 and 4 to 9 is patentable over all cited references each taken alone or in combination.

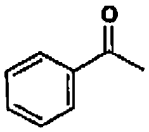
Claims 1 and 2 are rejected under 35 U.S.C. 102(b) as being anticipated by Costello et al (WO99/23242).

The Examiner contends that "Costello et al., discloses a method of using ketoreductase to reduce ketone compounds and refers to compound No. 7 in Table 1. The method can be performed using the enzyme or whole cell conversion using a microorganism expressing the enzyme."

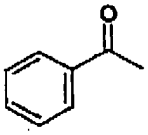
It is submitted that Applicants' process as claimed in Claims 1 and 2 is patentable over Costello et al.

Costello et al discloses use of the ketoreductase enzyme from Z. rouxii in a process for reduction of ketones.

In Table 1 entitled "Substrate specificity of ketoreductase from Z. rouxii," at page 9, Costello et al. disclose the ketone



(compound 7)

and a relative activity of 4%. Thus, only 4% of the ketone  undergoes reduction.

Claim 1 has been amended to define the enzyme as defined in original Claim 3, that is, the *Pichia methanolica* ketoreductase of Figure 1 as expressed in Escherichia coli.

Claim 2 has been amended to define the microorganism as set and in the Table at page 14 of the Specification.

There is no disclosure or suggestion in Costello et al of any of the enzymes or microorganisms claimed by the Applicants. In addition, the ketone defined in Applicants Claims 1 and 2 include X and Y substituents not present in the Costello et al ketone. In fact, the Costello et al ketone 7 and also ketone 8 include an unsubstituted phenyl ring, whereas the phenyl ring present in Applicants' ketone must include an X substituent which is other than H, and a Y substituent which is other than H. Thus, the process disclosed by Costello et al involves reduction of an unsubstituted ketone, which is different from X-and Y- substituted ketones employed in Applicants' process as claimed, and a microorganism which is different from the enzyme and /or microorganisms employed in Applicants' process as claimed, to produce an alcohol product which is different from Applicants' alcohol product as claimed. Thus, the Costello et al process is completely different from Applicants' process as claimed. The differences between the Costello et al process and Applicants' process are unobvious material and significant differences which clearly support Applicants' position that Applicants' process as now claimed in Claims 1 and 2 is patentable over Costello et al.

In essence, the Examiner has as much indicated that Claims 1 and 2 as now amended are patentable over Costello et al taken alone inasmuch as Claims 3 and 4 have not been rejected over Costello et al. Claim 1 as amended is now a combination of Claims 1and 3 and Claim 2 as amended is essentially a combination of Claims 2 and 4 (with additional microorganisms not disclosed or suggested by Costello et al). Thus, Claims 1 and 2 as now amended are patentable

over Costello et al taken alone for the same reasons that original Claims 3 and 4 are patentable over Costello et al., taken are alone.

In view of the foregoing, it is submitted that Claims 1 and 2 and the remaining Claims 4 to 9 are patentable over Costello et al.

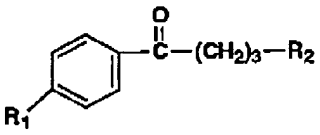
Claims 3 and 4 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Costello et al (WO99/23242) in view of Patel et al (U.S. Patent No. 5,393,663).

> The Examiner states that "while the reference [Costello et al] discloses a sequence of the enzyme employed and the expression of the enzyme in an E. Coli host, the reference is silent as to the use of a *Pichia methanolica* source for the enzyme.
>
> "The reference of Patel et al discloses that *Pichia methanolica* ATCC 56508 is a known source for a ketoreductase for converting a ketone compound into an S-enantiomer compound (see Table 2)."
>
> The Examiner concludes that "in view of this teaching, it would have been obvious to one of ordinary skill in the art to determine the optimum source of the enzyme from known sources based on considerations such as cost, availability and/or the specifics of the substrate intended to be converted while maintaining the efficiency of the conversion system. If the sequence of ATCC 56508 is not the same as that of Figure 1 of this instant application, those skilled in the art will recognize that numerous silent substitutions of nucleotide base pairs could be introduced into the sequence without altering the identity of the encoded protein product."

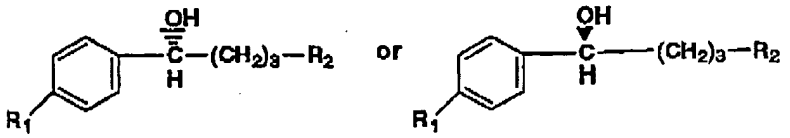
It is submitted that Applicants' process as claimed in Claim 1 (which is now a combination of Claims 1 and 3) and Claim 2 (which is in essence a combination of Claims 2 and 4 and more) and the remaining Claims 4 to 9 are patentable over Costello et al taken in view after Patel et al.

The comments set above with regard to Costello et al apply here as well.

U.S. Patent No. 5,393,663 to Patel et al discloses a process for selectively reducing a ketone of the structure



to form the alcohol of the structure

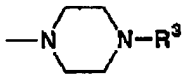


by treating the ketone with "an oxido-reductase or a microorganism comprising an oxido-reductas " (Column 1, lines 60 to 62).

in the above formula,

R^1 is halogen (fluorine preferred),

R^2 is halogen (chlorine preferred), alkyl, cycloalkyl, aryl or



Patel et al discloses a number of microorganism including Candida boilidini, Geotrichum candidum, Hansenula polymorpha, Nocardia salmonicolor, Saccharomyces cerevisiae (baker's yeast) as well as *Pichia methanolica* ATCC56508 (Table 2-Col. 7 and 8).

It is submitted that Applicants' process as now claimed is patentable over Patel et al taken alone.

Patel et al teaches selective reduction of a ketone which is completely different from the ketone employed in Applicants' process. The Patel et al ketone includes a phenyl ring with a single substituent. Applicants' ketone must include an X substituent and a Y substituent. The Patel et al ketone includes a $-(CH_2)_3-R_2$ group linked to the carbonyl group. Applicants' ketone includes a methyl group linked to the carbonyl group.

The fact that the above microorganisms are effective in reducing the Patel et al ketones to the corresponding alcohol would not suggest or motivate one skilled in the art, absent the use of hindsight in view of Applicants' disclosure, to employ such microorganisms in attempting to reduce Applicants' ketone to the corresponding alcohol. There are major differences between Applicants' ketone and the Patel et al ketone, as pointed out above, which differences are unobvious, and which differences would not make it obvious to replace the Patel et al ketone to with Applicants' ketone and expect that Applicants' ketone would be effectively reduced to the corresponding desired alcohol.

In view of the above, it is submitted that Applicants' process as claimed in Claims 1, 2 and 4 to 10 as amended is patentable over Patel et al.

It is also submitted that Applicants' process as claimed is patentable over a combination of Costello et al taken with Patel et al. Costello et al discloses a process employing a ketone, which is substantially and unobviously different from Applicants' ketone. The Costello et al ketone is unsubstituted while Applicants' ketone must include an X-substituent and a Y-substituent.

In addition, Costello et al employs a microorganism that is completely different from and thus does not make use of Applicants' microorganisms obvious. Even if the Patel et al microorganisms were substituted for the Costello et al Z. rouxil microorganism, the Costello et al process would still not make Applicants' process obvious in the view of the differences in the starting ketones as

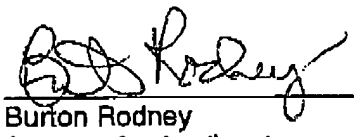
discussed above. Moreover there is nothing in either Costello et al or Patel et al which would suggest or motivate one skilled in the art to replace the Costello et al Z. rouxii with any of the Patel et al microorganisms. There is nothing that links these references. Each reference discloses different ketones and different microorganisms. Thus, absent the use of hindsight in view of Applicants' disclosure, there would be no reason for one skilled in the art to combine the teachings of these references. Thus, the cited combination of references amount to a hindsight combination and thus are improper and should be withdrawn.

At best the references might suggest to one skilled in the art to try replacing the Costello et al microorganism with the Patel et al microorganism. However, even if this were done, the combined process would still not make Applicants' process obvious for the reasons set out above. Furthermore, even if the microorganisms were substituted, there is no suggestion, disclosure or indication that they would work on the Costello et al substrate to convert the ketone to the alcohol. Again, even if this did work, it still would not make Applicants' process as claimed obvious or that it would be obvious that substitution of Applicants' ketones would be successful to produce the claimed alcohol.

In view of the foregoing, it is submitted that Applicants' process as claimed in Claims 1, 2 and 4 to 10 are patentable over a combination of Costello et al taken with Patel et al.

Inasmuch as it is clear that Claims 1, 2 and 4 to 10 are patentable over the cited references each taken alone or in combination, it is submitted Claims 1, 2 and 4 to 10 are in condition for allowance.

Respectfully submitted,



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